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# European Code against Cancer 4th Edition

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# European Code against Cancer 4th Edition: Medical exposures, including hormone therapy, and cancer☆

Søren Friis[a,b], Ausrele Kesminiene[c], Carolina Espina[c], Anssi Auvinen[d,e], Kurt Straif[c], Joachim Schüz[c,*]

[a] Danish Cancer Society Research Center, Danish Cancer Society, Strandboulevarden 49, 2100 Copenhagen, Denmark
[b] Department of Public Health, University of Copenhagen, 2100 Copenhagen, and Department of Clinical Epidemiology, Faculty of Health, Aarhus University Hospital, 8200 Aarhus N, Denmark
[c] International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, 69372 Lyon, France
[d] School of Health Sciences, University of Tampere, FI-33014 Tampere, Finland
[e] STUK—Radiation and Nuclear Safety Authority, Research and Environmental Surveillance, FI-00881 Helsinki, Finland

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ABSTRACT

The 4th edition of the European Code against Cancer recommends limiting – or avoiding when possible – the use of hormone replacement therapy (HRT) because of the increased risk of cancer, nevertheless acknowledging that prescription of HRT may be indicated under certain medical conditions. Current evidence shows that HRT, generally prescribed as menopausal hormone therapy, is associated with an increased risk of cancers of the breast, endometrium, and ovary, with the risk pattern depending on factors such as the type of therapy (oestrogen-only or combined oestrogen–progestogen), duration of treatment, and initiation according to the time of menopause. Carcinogenicity has also been established for anti-neoplastic agents used in cancer therapy, immunosuppressants, oestrogen–progestogen contraceptives, and tamoxifen. Medical use of ionising radiation, an established carcinogen, can provide major health benefits; however, prudent practices need to be in place, with procedures and techniques providing the needed diagnostic information or therapeutic gain with the lowest possible radiation exposure. For pharmaceutical drugs and medical radiation exposure with convincing evidence on their carcinogenicity, health benefits have to be balanced against the risks; potential increases in long-term cancer risk should be considered in the context of the often substantial and immediate health benefits from diagnosis and/or treatment. Thus, apart from HRT, no general recommendations on reducing cancer risk were given for carcinogenic drugs and medical radiation in the 4th edition of European Code against Cancer. It is crucial that the application of these measures relies on medical expertise and thorough benefit–risk evaluation. This also pertains to cancer-preventive drugs, and self-medication with aspirin or other potential chemopreventive drugs is strongly discouraged because of the possibility of serious, potentially lethal, adverse events.

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## 1. MEDICAL EXPOSURES

### 1.1. Introduction

The 4th revision of the European Code against Cancer (Box 1) aims to give recommendations to reduce the risk of cancer through personal behavioural changes or participation in organised intervention programmes [1]. In this context, medical exposures differ from recommendations regarding, for example, smoking, sun exposure, or dietary habits, since most medical exposures are not controlled by the individual but administered as diagnostic or therapeutic measures by healthcare professionals. Therefore,

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* Corresponding author at: IARC European Code against Cancer Secretariat, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France.
*E-mail address:* secretariat-cancer-code-europe@iarc.fr (J. Schüz).

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**Box 1.** European Code Against Cancer

EUROPEAN CODE AGAINST CANCER

12 ways to reduce your cancer risk

1 Do not smoke. Do not use any form of tobacco.

2 Make your home smoke free. Support smoke-free policies in your workplace.

3 Take action to be a healthy body weight.

4 Be physically active in everyday life. Limit the time you spend sitting.

5 Have a healthy diet:
- Eat plenty of whole grains, pulses, vegetables and fruits.
- Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks.
- Avoid processed meat; limit red meat and foods high in salt.

6 If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.

7 Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds.

8 In the workplace, protect yourself against cancer-causing substances by following health and safety instructions.

9 Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.

10 For women:
- Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby.
- Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT.

11 Ensure your children take part in vaccination programmes for:
- Hepatitis B (for newborns).
- Human papillomavirus (HPV) (for girls).

12 Take part in organized cancer screening programmes for:
- Bowel cancer (men and women).
- Breast cancer (women).
- Cervical cancer (women).

The European Code against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

although the target population for the European Code against Cancer is the general public, guidance on medical exposures should also be directed toward healthcare professionals. A new challenge is the increasing accessibility of drugs through web-based providers, typically without oversight by healthcare professionals or proper instructions for use.

Medical exposures encompass pharmaceutical drugs and the use of ionising radiation in medical diagnostics or therapy. In use of pharmaceutical drugs or ionising radiation, potential increases in the long-term risk of cancer or other adverse effects need to be considered in the context of health benefits – often substantial and immediate – from diagnosis and/or treatment. Chemotherapy and radiotherapy represent classical examples of the need for such careful benefit/risk evaluations, since both types of therapy may induce development of second malignancies, besides their ability to improve survival from the primary cancer being treated. For measures of screening and prevention, the benefit/risk ratio is generally lower than for therapeutic measures: e.g. in the use of X-rays in routine health checks or in the use of tamoxifen for breast cancer prevention. For all new medical interventions, the benefits should be demonstrated by rigorous research, ideally by randomised trials.

The primary objective of the present review was to provide the scientific justification for the recommendation on hormone replacement therapy (HRT), today predominantly prescribed as menopausal hormone therapy (and evaluated as such in the review), for which the Code recommends: "Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT". This recommendation is based on unequivocal scientific evidence that HRT is carcinogenic to humans and may induce cancers in female genital organs and breast [2,3]. Although treatment with HRT remains justified under certain medical conditions, the general population should be informed about the cancer risk and avoiding use of HRT outside defined indications. Carcinogenicity has also been established for several other medical exposures, including medications other than HRT and medical use of ionising radiation; however, no general recommendations were given for these measures in the 4th edition of the European Code against Cancer as their use relies on medical expertise and thorough benefit–risk evaluation in each individual.

### 1.2. Pharmaceutical drugs

A number of drugs used in medical practice have been established as carcinogenic to humans [3]. Some of these drugs – e.g. anti-neoplastic agents – exhibit a high benefit–risk ratio under the approved indications, and continued use of these drugs is endorsed [4]. In contrast, a decision to prescribe and use any drug with established or probable carcinogenicity (e.g. HRT) for non-life-threatening conditions is more problematic [5,6]. Irrespective of drug type and indication, it is imperative to monitor potential long-term carcinogenicity of drugs, because of the limited evidence of carcinogenic potential at the time of licensing. At that time, knowledge of the carcinogenic potential is based almost exclusively on preclinical studies, since the pre-marketing randomised clinical trials with limited sample sizes and follow-up are not well suited to the study of rare outcomes such as cancer, which typically has a long latency period [7–9]. Several drugs have been evaluated for potential cancer-preventive properties: i.e. their ability to interrupt mechanisms or pathways that initiate or accelerate development of cancer [10,11]. Currently, only a few drugs have been approved for cancer preventive therapy: e.g. tamoxifen for women at high risk of breast cancer. However, several drugs are under evaluation as preventive or adjuvant therapies against cancer, including for example aromatase inhibitors, aspirin, metformin, and statins [9].

### 1.3. Medical exposure to ionising radiation

Since the discovery of x-rays and radioactivity, radiation has been extensively utilised in medicine. Radiation has an important role in both diagnosis and treatment of a wide range of diseases, including cancer. The major medical applications of radiation include radiology, radiotherapy and nuclear medicine. Developments in medical imaging – particularly in computed tomography (CT) and its combinations with other imaging techniques – have led to substantial increases in relatively high-dose X-ray examinations. Medical radiation has become the second most important source of exposure to radiation for an average European citizen, after exposure to radon in homes [12]. To alert health professionals about potentially higher doses received by patients from some of the diagnostic procedures, the European Union Euratom directive 97/43 categorised CT and interventional radiology as procedures that expose patients to high doses of radiation. For illustration, a

typical chest CT gives a radiation dose equivalent to 400 chest radiographs (chest tomography 8 mSv; chest radiography 0.02 mSv) [13].

## 2. Cancer association with medical exposures

### 2.1. Carcinogenicity of hormonal therapy and other pharmaceutical drugs

Starting in the 1970s, the International Agency for Research on Cancer (IARC) has evaluated a wide range of drug exposures to assess their carcinogenic effects in humans, based on comprehensive literature reviews by expert committees [14]. In a recent volume (100A) of the Monographs Programme, the IARC reaffirmed the categorisation as carcinogenic to humans (Group 1) for 20 pharmaceutical agents and upgraded three agents from Group 2A (probably carcinogenic to humans) to Group 1 [3]. The latter included phenacetin per se, which was previously classified as a Group 1 agent only as part of "analgesic mixtures containing phenacetin". The majority of the Group 1 agents derive from two therapeutic categories: hormonal therapy and anti-neoplastic therapy (Tables 1 and 2).

#### 2.1.1. Menopausal hormone therapy

HRT includes various forms, doses, and regimens of oestrogen, either alone or combined with progestogen [15]. Oestrogen-only therapy was introduced in the 1960s, and its use increased until the mid-1970s, when evidence indicated a strong association between HRT and endometrial cancer [16,17]. Then, among non-hysterectomised women, the oestrogen-only regimen was replaced by combined oestrogen–progestogen therapy [18], which was used increasingly through the 1980s and 1990s [16,17]. Despite concern about the potential for increased risk of breast cancer [19], it was generally believed that HRT was associated with a net health benefit, which included prevention of cardiovascular disease [20]. However, this view changed dramatically in 2002, when the first results from the Women's Health Initiative (WHI) clinical trial [21,22] contrasted with findings from many observational studies [23]. Among 16,608 women aged 50–70 years at baseline, use of combined oestrogen–progestogen treatment was associated with a risk ratio (RR) for coronary heart disease of 1.24 (95% confidence interval [CI]: 1.00–1.54) compared to placebo, after a mean follow-up of 5.2 years [21,22]. A similar WHI trial included 10,739 women, aged 50–79 years and with prior hysterectomy, who were randomised to oestrogen-only therapy or placebo [24]. Both WHI trials were halted prematurely, because interim analyses indicated that the risks of both oestrogen regimens outweighed their benefits [21,24].

The WHI study was followed by reports of sharp declines in breast cancer incidence in both the United States and Europe [25–27]. This trend has been interpreted to be a direct result of modified recommendations for menopausal hormone therapy [28–30], although this has been met with some scepticism [31].

Recently, healthcare agencies in the United States and Europe have concluded that HRT is not suitable for primary prevention of chronic diseases [32–35]. Although there is some evidence that use of HRT protects against cardiovascular disease if started early in menopause [36,37], a recent Cochrane review of 19 cardiovascular trials concluded that use of HRT in postmenopausal women overall "has little if any benefit" in either primary or secondary prevention of cardiovascular disease, and causes an increase in the risk of stroke and venous thromboembolic events [38]. Thus, HRT should primarily be used for the short-term treatment of menopausal symptoms [32–35]. There is no consensus, however, on the definition of "short-term", and there are unresolved questions about the influence of menopausal hormone therapies on risks of specific cancer types.

*2.1.1.1. Breast cancer.* Based on a large body of evidence, the IARC has concluded that long-term use of combined oestrogen–progestogen HRT is associated with an increased risk of breast cancer (Table 1) [3]. The initial WHI study reported an RR of 1.26 (CI: 1.00–1.59) for breast cancer associated with the use of oestrogen–progestogen therapy [21], but patients in the oestrogen-only arm of the WHI study experienced a reduced risk of breast cancer (RR 0.77; CI: 0.59–1.01) [24]. Numerous observational studies have reported that HRT is associated with an increased risk of breast cancer, and generally associations have been stronger and more consistent for combined oestrogen–progestogen menopausal therapy than for oestrogen-only therapy [19,39–44]. In the Million Women Study in the United Kingdom (UK) [39,43], women were younger (average age 55.9 years) at cohort entry (1996–2001) than participants in the WHI study (average age 64 years) [21], enabling a more comprehensive evaluation of the impact of timing on HRT [43]. While the results of the two studies were similar for oestrogen–progestogen therapy, the Million Women Study found an increased risk of breast cancer with oestrogen-only therapy [39,43], in contrast to the inverse association observed in the WHI Study [24]. Additional analyses of the two studies have indicated that the risk differences observed

**Table 1**
Hormonal treatments assessed by the IARC Monographs Programme.

| Carcinogenic agent | Cancer sites with sufficient evidence of carcinogenicity in humans | Cancer sites where risk is reduced | Established mechanisms | Other likely mechanisms |
|---|---|---|---|---|
| Combined oestrogen–progestogen menopausal therapy | Endometrium (risk decreases with number of days per month of progestogen use); breast | – | Receptor-mediated events | Oestrogen genotoxicity |
| Oestrogen-only menopausal therapy | Endometrium, ovary (Limited evidence: breast) | – | Oestrogen receptor-mediated events | Genotoxicity |
| Combined oestrogen–progestogen oral contraceptives | Breast, cervix, liver (hepatocellular carcinoma) | Endometrium, ovary | Receptor-mediated events | Oestrogen genotoxicity; hormone-stimulated expression of human papilloma virus genes |
| Diethylstilbestrol | Breast (exposure during pregnancy), vagina and cervix (clear-cell adenocarcinoma; exposure in utero) [Limited evidence; endometrium (exposure during pregnancy), cervix (squamous carcinoma; exposure in utero), testis (exposure in utero)] | – | Oestrogen-receptor-mediated events (vagina, cervix), genotoxicity | Epigenetic programming |
| Tamoxifen | Endometrium | Breast | Oestrogen-receptor-mediated events, genotoxicity | – |

**Table 2**
Anti-neoplastic drugs and other drugs evaluated by the IARC Monographs Programme.

| Group 1 agent | Cancer sites with sufficient evidence of carcinogenicity in humans | Established mechanisms |
|---|---|---|
| Anti-neoplastic agents | | |
| Busulfan | Acute myeloid leukaemia | Genotoxicity (alkylating agent) |
| Chlorambucil | Acute myeloid leukaemia | Genotoxicity (alkylating agent) |
| Chlornaphazine | Urinary bladder | Genotoxicity (alkylating agent, metabolism to 2-naphthylamine derivatives) |
| Cyclophosphamide | Acute myeloid leukaemia, urinary bladder | Genotoxicity (metabolism to alkylating agents) |
| Etoposide (Group 2A in 2000) | [Limited evidence: acute myeloid leukaemia] | Genotoxicity, translocations involving *MLL* gene |
| Etoposide in combination with cisplatin and bleomycin | Acute myeloid leukaemia | Genotoxicity, translocations involving *MLL* gene (etoposide) |
| Melphalan | Acute myeloid leukaemia | Genotoxicity (alkylating agent) |
| MOPP[a] combined chemotherapy | Acute myeloid leukaemia, lung | Genotoxicity |
| Semustine (methyl-CCNU) | Acute myeloid leukaemia | Genotoxicity (alkylating agent) |
| Thiotepa | Leukaemia | Genotoxicity (alkylating agent) |
| Treosulfan | Acute myeloid leukaemia | Genotoxicity (alkylating agent) |
| Immunosuppressive agents | | |
| Azathioprine | Non-Hodgkin lymphoma, skin | Genotoxicity, immunosuppression |
| Cyclosporin | Non-Hodgkin lymphoma, skin, multiple other sites | Immunosuppression |
| Other carcinogenic agents | | |
| Analgesic mixtures containing phenacetin | Renal pelvis, ureter | (See phenacetin in text) |
| Aristolochic acid (Group 2A in 2002) | – | Genotoxicity, DNA adducts in animals are the same as those found in humans exposed to plants, A:T → T:A transversions in *TP53*; *RAS* activation |
| Methoxsalen plus ultraviolet A radiation | Skin | Genotoxicity following photo-activation |
| Phenacetin (Group 2A in 1987) | Renal pelvis, ureter | Genotoxicity, cell proliferation |
| Plants containing aristolochic acid | Renal pelvis, ureter | Genotoxicity, DNA adducts in humans, A:T → T:A transversions in *TP53* in human tumours |

[a] Chlormethine (mechlorethamine), vincristine (oncovin), procarbazine, and prednisone.

for oestrogen-only therapy may be explained by differences in age distribution and anthropometric measures [43,45–47]. In a recent update of the Million Women Study, the use of oestrogen-only agents was associated with a 43% increase in the risk of breast cancer (RR 1.43; CI: 1.35–1.51) when treatment had begun less than 5 years after menopause; however, when oestrogen-only therapy was initiated 5 years or more after menopause, there was no influence on breast cancer risk (RR 1.05; CI: 0.89–1.24) [43]. A similar tendency was observed in the WHI study; breast cancer risk was reduced among women who first started oestrogen-only therapy 5 years or more after menopause (HR 0.65; CI: 0.48–0.89), whereas the association was close to unity among women who initiated treatment closer to menopause (HR 0.89; CI: 0.66–1.20) [48]. Thus, oestrogen-only therapy may be associated with a neutral or increased risk of breast cancer when started close to the time of menopause, but when started later in menopause it may be associated with a neutral or even reduced breast cancer risk [43,47–49]. In addition, in both the Million Women Study and the WHI study, breast cancer risk associated with oestrogen-only therapy was higher among women with a low body mass index than among overweight or obese women [50,51]. Since women in the WHI study had on average higher body mass index than women in the Million Women Study, this contributes to an explanation of the difference in overall findings for oestrogen-only therapy and breast cancer risk in these two landmark studies [47].

The relationship between HRT and breast cancer risk is thus complex and varies with age at menopause, age at initiation of hormone therapy, anthropometric measures, and other breast cancer risk factors [47,52–55]. Moreover, there is no clear consensus about when to discontinue HRT, if started at normal menopause [32–35]. Notwithstanding the uncertainties, the current evidence indicates that breast cancer risk associated with the use of HRT is higher when treatment is started close to menopause [43,47,51,56]; it occurs after a few years of treatment [21,28,39,43,57]; it increases with treatment duration [43,58–61]; and it declines within a few years after treatment cessation [58,62].

*2.1.1.2. Endometrial cancer.* Oestrogen-only menopausal therapy is known to induce endometrial hyperplasia and cancer (Table 1) [63]. The excess risk depends on the dose of oestrogen and treatment duration; reports vary between two-fold and ten-fold risk elevations [64,65]. Current evidence indicates that continuous combined oestrogen–progestogen regimens may be associated with a neutral or even reduced risk of endometrial cancer, whereas sequential regimens may impose an increased risk when the progestogen component is prescribed for less than 10–15 days per month [66–69]. A recent meta-analysis of observational studies reported a risk reduction of endometrial cancer with continuous (>25 days per month) oestrogen–progestogen therapy (pooled RR 0.78; CI: 0.72–0.86) [69]. The corresponding RR for sequential oestrogen–progestogen therapy with less than 10 days progestogen per month was 1.76 (CI: 1.51–2.05); in contrast, there was no association with regimens with 10–24 days of simultaneous oestrogen–progestin administration (RR 1.07; CI: 0.92–1.24) [69]. It is unclear whether the suggested reduced risk of endometrial cancer associated with continuous oestrogen–progestogen regimens persists with long-term use. Unresolved issues also include the influence of oestrogen or progestogen dosages, mode of administration, and potential risk variations for different types of endometrial cancer [69].

*2.1.1.3. Ovarian cancer.* In the 100A volume of the Monographs Programme, the IARC concluded that oestrogen-only hormone therapy is causally associated with an increased risk of ovarian cancer (Table 1), whereas data to support any firm conclusions on combined oestrogen–progestogen agents were regarded as

inadequate [3]. A meta-analysis on 13 studies reported slightly increased pooled RRs for ovarian cancer for each 5 years of oestrogen-only or oestrogen–progestogen treatment (1.22, CI: 1.18–1.27; and 1.10, CI: 1.04–1.16, respectively) [70]. Those findings were consistent with recent large observational studies that were not included in the meta-analysis [71,72]. Most recently, the Collaborative Group on Epidemiological Studies of Ovarian Cancer reported the results of a meta-analysis of 52 epidemiological studies of HRT use and ovarian cancer risk [73]. The authors focused on 17 "prospective" studies for which they found a pooled RR for ovarian cancer of 1.20 (CI: 1.15–1.26) associated with ever-use of HRT compared to never-use. The association was strongest among current users of HRT (RR 1.41; 1.32–1.50), with no difference between women who had used HRT for less than 5 years (1.43) and those with more 5 years of use (1.41). In accordance with previous studies [71,72,74], substantial risk differences were seen according to the type of ovarian cancer, with increased RRs for serous and endometrioid carcinomas and neutral to decreased RRs for mucinous and clear-cell carcinomas [73]. The results were similar for oestrogen-only and oestrogen–progestogen therapy. Based on the results of the meta-analysis, the authors estimated that 5 years of use of HRT from around age 50 years would result in one additional ovarian cancer case per 1000 users and one additional ovarian cancer death per 1700 users. However, some have questioned the validity of these estimates and the existence of a causal relationship between oestrogen–progestogen therapy and ovarian cancer risk, arguing that the findings in the meta-analysis of no duration-risk relationship, similar results for oestrogen-only and oestrogen-progestogen therapy, and null associations for "retrospective studies", are not readily compatible with a cause-and-effect relationship between HRT and ovarian cancer risk [75].

*2.1.1.4. Other cancers.* At least six meta-analyses have reported that HRT is associated with a decreased risk of colorectal cancer [76–81]; however, individual studies show considerable variation, and little risk variation has been observed with different therapy durations [76,77,79–81]. Only two meta-analyses presented separate results for oestrogen-only and oestrogen–progestogen therapies, showing similar and largest risk reductions (20–30%) in colorectal cancer risk among women currently using oestrogen-only or oestrogen–progestogen therapy [79,80].

Experimental, clinical, and epidemiological studies have suggested that HRT may increase the risk of meningioma [82–86], but decrease the risk of cancers in the upper gastrointestinal tract or lung [80,87–89]. The results for lung cancer may be influenced by negative confounding by smoking, and updates of the WHI Study did not support a protective effect of either oestrogen-only or oestrogen–progestogen therapy against lung cancer [90,91].

*2.1.2. Hormonal contraceptives*

Globally, millions of women of reproductive age use hormonal contraceptives, and contraceptive use is increasing, notably in developing countries [92]. Numerous types and preparations of hormonal contraceptives have been marketed since the late 1950s [17,93]. Currently, most contraceptives are oral oestrogen–progestogen combinations [94]. Based on numerous epidemiological studies and comprehensive laboratory data, the IARC has concluded that combined oestrogen–progestogen oral contraceptives increase the risk of cancers of the breast, cervix, and liver, and reduce the risk of ovarian and endometrial cancer (Table 1) [2,3,95–97]. Meta-analyses have reported pooled overall RRs from 1.07 to 1.24 for associations between oral contraceptives and breast cancer, with higher RRs for associations between long-term contraceptive use and risk of premenopausal breast cancer [98–100]. However, breast cancer risk associated with oral contraceptives has been consistently reported to approach unity at 5–10 years after discontinuation [96]: i.e. oral contraceptives have only limited influence on the incidence of post-menopausal breast cancer. For cervical cancer, a comprehensive meta-analysis of 24 epidemiological studies reported pooled RRs of 0.96, 1.20, and 1.56 for invasive cervical cancer associated with oral contraceptive use for, respectively, $<5$ years, 5–9 years, and $\geq 10$ years [101]. After discontinuation of oral contraceptives, the RRs declined from 1.65 among current users to 1.05 among women who discontinued use for 10–14 years. Finally, the IARC has also concluded that long-term use of combined oral contraceptives induces hepatocellular carcinoma in populations with low prevalence of hepatitis B infection and chronic liver disease [3]. A meta-analysis of 12 case–control studies reported an RR of 1.57 (CI: 0.96–2.45) for hepatocellular carcinoma associated with ever use of oral contraceptives. Individual studies ($n = 6$) found that long duration of oral contraceptive use was associated with up to a 20-fold increased risk of hepatocellular carcinoma, indicating a strong duration–response relationship, although the statistical precision was limited in the individual studies [102].

Notwithstanding the adverse effects of oestrogen–progestogen contraceptives [3,103], the net public health effect of these agents is beneficial, because they can prevent ovarian and endometrial cancer, unwanted pregnancies and induced abortions [96]. A recent comprehensive meta-analysis of 55 studies reported a pooled RR for ovarian cancer of 0.73 (CI: 0.66–0.81) associated with ever use of oral contraceptives, and over 50% risk reduction with $\geq 10$ years use [104]. Epidemiological studies have consistently shown that women who have ever used oestrogen–progestogen oral contraceptives have an about 50% reduced risk of endometrial cancer compared to women who have never used contraceptives [3,96,105]. Several studies have also suggested that combined oestrogen–progestogen contraceptives may reduce the risk of colorectal cancer; however, this evidence is not conclusive [3].

A complete literature review of the influence of oral contraceptives on cancer risk is outside the scope of the present paper; however, comprehensive reviews are available in previous IARC Monographs [2,3] and several meta-analyses [88,96,98–102,104–120].

*2.1.3. Tamoxifen*

The anti-oestrogen, tamoxifen, possesses both carcinogenic and cancer preventive properties [3]. Tamoxifen is indicated as an adjuvant therapy for postmenopausal, oestrogen-receptor-positive breast cancer and ductal carcinoma in situ [7,17]. Furthermore, tamoxifen has been approved as a breast cancer preventive agent among women at high risk of developing breast cancer (see section 2.2.1) [121,122]. Observational studies and randomised trials have consistently shown that use of tamoxifen is associated with approximately a two-fold increased risk of endometrial cancer, whether given as adjuvant therapy or as a preventive therapy [3,7,121,122].

*2.1.4. Anti-neoplastic therapies*

Anti-neoplastic drugs may induce secondary cancer after curing a primary cancer in children, adolescents [123], and adults [124]. However, the high rate of increased survival or related beneficial outcome with anti-neoplastic drugs outweighs the risk of developing secondary cancers; thus, these drugs are endorsed in clinical practice [125]. Eleven of these agents or combination therapies have been classified as carcinogenic to humans by the IARC (Table 2) [3,14,126]. Of these, the majority are alkylating agents that exhibit genotoxicity, primarily through alkylation of purine bases in DNA [127,128]. Typically, these agents induce acute myeloid leukaemia, which often involves the clonal loss of either

chromosome 5 or 7, although gene translocations also occur (Table 2) [127–129]. In addition to leukaemia risk, alkylating chemotherapy has been related to development of solid tumours, notably cancers of the lung or urinary bladder (Table 2) [125,129,130]. Several traditional anti-neoplastic drugs have been supplemented or superseded by newer drugs [93,125], and research continues to seek ways to reduce dosage or develop safer, more effective replacement products [125,131].

#### 2.1.5. Immunosuppressive agents

Immunosuppressive agents (Table 2) are typically used to treat serious chronic conditions such as suppression of host-versus-graft reactions and rejections of transplants, haematological diseases, rheumatological diseases, and inflammatory bowel disease [132,133]. Their carcinogenic mechanisms are related to immunosuppression rather than genotoxicity [3,134,135]. Evidence that immunosuppressant agents are carcinogenic derives primarily from studies on organ transplantation (Table 1) [136–138]. Specifically, there is sufficient evidence that immunosuppressants induce non-melanoma skin cancer and non-Hodgkin's lymphoma. Generally, the benefits of these drugs outweigh their carcinogenicity [134].

#### 2.1.6. Other carcinogenic pharmaceuticals

Phenacetin and phenacetin-containing mixtures induce cancers of the renal pelvis and ureter (Table 2) [3]. Although phenacetin was withdrawn from the market in most countries around 1980 [3], a lasting impact of these agents cannot yet be excluded due to the long latency for development of some types of cancer, and relevant cancers may be diagnosed in future. *Aristolochia* plants or seeds are typically used in Chinese herbal preparations, but have also been found in slimming products used in a Belgian weight loss clinic, as well as in flour used in bread and cereals in the Balkans [3,139,140]. Aristolochic acid was identified as the carcinogenic agent shortly after the first IARC classification of herbal remedies containing plant species of the genus *Aristolochia*; on the basis of aristolochic-acid-specific DNA mutations in patients with nephropathia or urothelial tumours who had ingested material from these plants species (Table 2) [3,140–142]. Although preparations containing *Aristolochia* seeds have been banned in Europe for over a decade, *Aristolochia* seeds are still detected occasionally in herb shipments to Europe [143]. Methoxsalen, a psoralen found in various plants, is a photosensitizer, used in conjunction with ultraviolet radiation phototherapy for various conditions [17,144]. Methoxsalen has been suspected to cause various types of skin cancer, but the association is only convincing for the combined application of methoxsalen with ultraviolet A radiation and squamous-cell carcinoma [145]. Photosensitivity is also induced by other frequently used drugs such as antihypertensives, hydrochlorothiazide (Table 3) and nifedipine, which are also suspected to increase the risk of lip and skin cancers [146].

Many of the drugs evaluated by the IARC have been categorised as probably (Group 2A) or possibly (Group 2B) carcinogenic to humans, because epidemiological evidence has not been definitive, or because carcinogenicity has been demonstrated only in experimental animals (Table 3). A discussion of these drugs is outside the scope of the present paper, other than to emphasise the importance of continued monitoring of carcinogenicity of pharmaceutical drugs.

### 2.2. Cancer preventive drugs

Cancer chemoprevention is defined as a pharmacological intervention, with drugs or nutrient components, which aims to prevent or inhibit the development of neoplasms [147]. Currently, only a few drugs have been approved for cancer chemoprevention: i.e. tamoxifen and raloxifene (anti-oestrogens) in prevention of breast cancer in pre- and post-menopausal women at high risk of developing breast cancer, and sulindac and celecoxib (non-aspirin non-steroidal anti-inflammatory drugs; NSAIDs) in prevention of colorectal cancer in patients with hereditary colorectal cancer syndromes [148,149]. However, several drug categories are considered definitely or potentially effective in primary chemoprevention, including hormone antagonists, aspirin, statins, metformin, and 5α-reductase inhibitors.

#### 2.2.1. Hormone antagonists

Several selective oestrogen-receptor modulators (SERMs) and aromatase inhibitors have been approved for endocrine therapy in women with hormone-receptor-positive breast cancer [150,151]. However, to date, only the two SERMs tamoxifen and raloxifene have been approved for preventive therapy in women at high risk of developing breast cancer [151,152]. A recent meta-analysis of nine breast cancer prevention trials reported an overall 38% reduction (RR 0.62; CI: 0.56–0.69) in breast cancer risk associated with the use of SERMs with a median follow-up of 5.4 years [152]; this effect was due solely to a decreased risk of oestrogen-receptor-positive breast cancer (RR 0.49; CI: 0.42–0.57). Recent studies have indicated that aromatase inhibitors, including exemestane and anastrozol, may have superior efficacy and safety compared to tamoxifen [153,154], but direct comparisons are lacking.

**Table 3**
Drugs classified as probably or possibly carcinogenic to humans (Group 2A or 2B, respectively) assessed by the IARC Monographs Programme.[a]

| Drug | Group | Monograph volumes | Year |
|---|---|---|---|
| Anabolic steroids | 2A | 10, Suppl. 7[b] | 1987 |
| Azacitidine | 2A | 50 | 1990 |
| Aziridine | 2B | 9, Suppl. 7[b], 71 | 1999 |
| Bleomycin | 2B | 26, Suppl. 7[b] | 1987 |
| Chloral | 2A | 63, 106 | 2015 |
| Chloral hydrate | 2A | 84, 106 | 2015 |
| Chloramphenicol | 2A | 50 | 1990 |
| Cisplatin | 2A | Suppl. 7[b] | 1987 |
| Dacarbazine | 2B | 26, Suppl. 7[b] | 1987 |
| Daunomycin | 2B | 10, Suppl. 7[b] | 1987 |
| Digoxin | 2B | 108 | 2015 |
| Griseofulvin | 2B | 79 | 2001 |
| Hydrochlorothiazide | 2B | 50, 108 | 2015 |
| Medroxyprogesterone acetate | 2B | 21, Suppl. 7[b] | 1987 |
| Merphalan | 2B | 9, Suppl. 7[a] | 1987 |
| Methylthiouracil | 2B | 79 | 2001 |
| Metronidazole | 2B | 13, Suppl. 7[b] | 1987 |
| Mitomycin C | 2B | 10, Suppl. 7[b] | 1987 |
| Mitoxantrone | 2B | 76 | 2000 |
| Oxazepam | 2B | 66 | 1996 |
| Pentosanpolysulphate sodium | 2B | 108 | 2015 |
| Phenazopyridine hydrochloride | 2B | 24, Suppl. 7[b] | 1987 |
| Phenobarbital | 2B | 79 | 2001 |
| Phenoxybenzamine hydrochloride | 2B | 24, Suppl. 7[b] | 1987 |
| Phenytoin | 2B | 66 | 1996 |
| Pioglitazone | 2A | 108 | 2015 |
| Primidone | 2B | 108 | 2015 |
| Procarbazine hydrochloride | 2A | 26, Suppl. 7[b] | 1987 |
| Progestins | 2B | Suppl. 7[a] | 1987 |
| Progestogen-only contraceptives | 2B | 72 | 1999 |
| Propylthiouracil | 2B | 79 | 2001 |
| Streptozotocin | 2B | 17, Suppl. 7[b] | 1987 |
| Sulfasalazine | 2B | 108 | 2015 |
| Teniposide | 2A | 76 | 2000 |
| Thiouracil | 2B | 79 | 2001 |
| Triamterene | 2B | 108 | 2015 |
| Zalcitabine | 2B | 76 | 2000 |
| Zidovudine | 2B | 76 | 2000 |

[a] http://monographs.iarc.fr/ENG/Classification/index.php.
[b] IARC monographs Supplement No 7. Overall evaluations of carcinogenicity: an updating of IARC monographs Volumes 1–42.

*2.2.2. Aspirin and other non-steroidal anti-inflammatory drugs*

A large collection of observational epidemiological studies [155–158], long-term follow-up for cancer of randomised primary prevention [159] or cardiovascular [160,161] trials, randomised trials on colon adenoma recurrence [162–166], and randomised trials in patients with hereditary colorectal cancer syndromes [167,168] have established that use of aspirin or other NSAIDs reduce the risk of colorectal neoplasia and cancer. There is also substantial evidence to suggest that use of aspirin or non-aspirin NSAIDs may protect against upper gastrointestinal cancers, including oesophageal and gastric cancer [158,169–172]. Meta-analyses of epidemiological studies have also indicated that NSAID use may protect against breast [158,173–175], lung [158,176,177], endometrial [178], ovarian [179,180] and prostate [158,181,182] cancers, but the reported inverse associations of NSAID use with these cancers are weaker than those demonstrated for gastroenterological cancers. The anti-neoplastic mechanisms of NSAIDs are not entirely clear, although the effect of non-aspirin NSAIDs appears to be clearly related to inhibition of cyclooxygenase enzymes [183–185]. The established association between non-aspirin NSAID use and cardiovascular events has impeded their potential in cancer prevention [186,187]; thus, evaluations of NSAID use in cancer prevention have focused on aspirin. Recently, Cuzick et al. published a comprehensive review of the role of aspirin in cancer prevention, based on data from systematic reviews and individual clinical or epidemiological studies of the beneficial effects (cancer, cardiovascular disease) or adverse events (gastrointestinal toxicity, haemorrhagic stroke) of aspirin [158]. The authors concluded that aspirin use for a minimum of 5 years at daily doses between 75 mg and 325 mg appears to have a favourable benefit–risk profile, notably among individuals between the ages of 50 and 65 years, and that longer use is likely to yield a greater benefit. The optimum regimen, however, remains to be determined [158]. In a pooled analysis of four randomised cardiovascular trials of aspirin, Rothwell et al. reported that daily doses of 75–300 mg during median intervention periods of 2.6–6.9 years reduced the 20-year risk of colon cancer by 24% and cancer-associated mortality by 35%, with 75 mg being as effective as higher doses [160]. Irrespective of study design, most studies indicate that a minimum of 5 years of consistent aspirin use is necessary to achieve a protective effect against colorectal cancer [156–158].

Several important questions remain unresolved regarding the association between aspirin use and cancer risk, including the optimum dose, duration of treatment, timing, and identification of individuals eligible for treatment [158,188]. Future studies and ongoing randomised trials are necessary to obtain conclusive data on these issues. Aspirin cannot be recommended for cancer prevention in the general healthy population because of the risk of serious adverse events: notably, upper gastrointestinal bleeding [189], although Cuzick et al. have recently argued that low-dose aspirin may be considered for prophylactic use against cancer in segments of the general population [158].

*2.2.3. Statins*

Increasing experimental evidence has suggested that statins may have anti-neoplastic effects [190–193]. However, several randomised trials with cancer as a secondary end-point have reported that 5–10 years of statin treatment did not reduce the risk of cancer, overall or at specific sites [191,194]. Likewise, observational epidemiological studies with longer follow-up have generally produced null results, except for slight inverse associations between statin use and risk of gastrointestinal cancer, hepatocellular carcinoma, and aggressive prostate cancer [191,192,194–205]. Statins have also been evaluated as an adjuvant to standard cancer therapy; however, to date this has yielded mainly null results [190,191,193]. Additional research should clarify whether statins have a future role in cancer prevention or therapy.

*2.2.4. Metformin*

Observational epidemiological studies and meta-analyses have reported that metformin, a widely used oral antidiabetic drug, may reduce the risk of several cancer types [206–216]. However, due to the complex nature of diabetes and the broad array of available therapies, it is difficult, in observational settings, to discern whether the inverse association between metformin and cancer risk is due to an anti-neoplastic effect of metformin or might result from uncontrolled confounding, when metformin is compared to other antidiabetics [208,216–218]. Several trials have recently been launched that aim to assess the potential of metformin for preventing cancer or cancer recurrence [208,215].

*2.2.5. Five-alpha reductase inhibitors*

Two large randomised trials have demonstrated that the two 5-alpha reductase inhibitors, finasteride and dutasteride, used for treating benign prostatic hyperplasia, reduced the overall risk of prostate cancer by 25% [219–221]. However, both studies also found an increased occurrence of aggressive prostate cancer among patients in the finasteride arm. It remains unclear whether the observed increased risk of aggressive prostate cancer is due to detection bias or a true biological association [219–221]. A recent 18-year update of the finasteride study reported results for risks of overall and aggressive prostate cancer compatible with those during the intervention [222]. Mortality was similar in the intervention and placebo arms, even when men were stratified into low- or high-grade prostate cancer at diagnosis, further complicating the interpretation of the effect of 5-alpha reductase inhibitors against prostate cancer. These results and uncertainties have hindered the use of 5-alpha reductase inhibitors as cancer preventive agents [221,223,224].

*2.3. Carcinogenicity of medical radiation*

DNA damage, which through DNA misrepair can lead to the development of cancer, is the most commonly recognised mechanism of radiation carcinogenesis. Ionising radiation has been classified by the IARC as an established (Group 1) carcinogen [225]. Key evidence for the carcinogenicity of ionising radiation has been reviewed by IARC, the United Nations Scientific Committee on the Effects of Atomic Radiation [226] and the International Commission on Radiological Protection [12,227].

*2.3.1. Therapeutic medical radiation*

The medical applications of ionising radiation include diagnostic examinations and therapy. Radiation treatment for benign diseases was relatively common until the 1960s. While these treatments were generally effective for benign diseases – such as ankylosing spondylitis, post-partum mastitis, peptic ulcer, skin haemangioma, tinea capitis, enlarged thymus gland, enlarged tonsils and acne – some treatments also resulted in enhanced cancer risks [228]. As new treatments have become available and more has been learned about radiation risks, the use of radiotherapy for benign disease has declined, whereas the use of radiotherapy in cancer patients has increased slowly over recent decades [229]. Cancer radiotherapy delivers high radiation doses to target organs or tissues of the order of tens of Grays (Gy) [229]. Numerous studies have revealed an increased incidence of second primary cancers after radiotherapy. These investigations include both large, comprehensive cohort studies and case–control studies [225]. In elderly radiotherapy patients, the excess occurrence of cancer is estimated to be 1.5% at 10 years after treatment and may appear both at sites adjacent to the radiated area and at sites

outside these areas [230]. Long-term survivors of childhood malignancies who underwent radiotherapy experience higher risks of brain tumours and breast cancer [226]. However, the precise localisations and risks of second cancers following radiation therapy is difficult to ascertain because radiotherapy is often combined with chemotherapy and the separate impact of these therapeutic measures is difficult to disentangle. Moreover, the cancer risk pattern among patients with previous cancers may differ from that of the general population for other reasons.

The impact of radiation-induced tumours in radiotherapy patients becomes increasingly important as better survival leads to more long-term survivors, and clinicians are becoming more aware of the potential long-term consequences of high-dose radiotherapy. As a result, radiotherapy doses have been reduced for Hodgkin's disease, testicular cancer, and breast cancer [231]. New technologies are being increasingly introduced, such as intensity-modulated radiation therapy (which allows changes in the intensity of the radiation beams during treatment sessions) and proton beam therapy with pencil scanning beam; these are highly targeted types of radiotherapy that can treat hard-to-reach cancers with a potentially lower risk of damaging the surrounding tissue and inducing second cancers [229].

*2.3.2. Diagnostic medical radiation*

Since 1956, epidemiological studies have linked diagnostic X-rays with increased cancer risk. Important findings include a modest increase in childhood leukaemia among the offspring of mothers who underwent pelvic X-rays during pregnancy [232,233], and an excess of breast cancer among women monitored with fluoroscopy for tuberculosis [231,234,235], or undergoing repeated X-rays for scoliosis [236].

Distinct benefits derive from the use of diagnostic x-rays and the potential cancer risk to an individual is small; it has been estimated that diagnostic X-ray use in the UK causes 0.6% of the cumulative risk of cancer to age 75 years [237]. Nevertheless, the large number of people exposed means that even small individual risks translate into a considerable number of cancer cases on a population level. This delicate balance between benefit and risk demands the judicious use of diagnostic radiation.

Diagnostic use of radiation is a rapidly changing field. During the past 30 years, newer imaging techniques – e.g. multi-slice CT, nuclear imaging, and PET-CT – have increased dramatically [229]. These procedures have increased the clinical benefit but have also resulted in higher radiation exposures to patients compared with exposures attributable to conventional radiography, for which average doses per examination have decreased with improved technology. Dramatic increase in the use of CT have raised concerns especially for paediatric patients, because children are more sensitive to harmful effects of ionising radiation and because CT protocols used for children, particularly in the past, were not always adjusted for smaller body size and therefore resulted in inappropriately high exposures. Recent studies in the UK and Australia have shown increased risks of childhood cancer, notably leukaemia and brain cancer, following CT examinations [238,239]. The UK study estimated that per 10,000 head CT scans at ages below 10 years, one extra case of leukaemia and one extra case of brain tumour will occur within 10 years after the CT scan [239]. The potential increase in future cancer occurrence attributable to the rapid expansion in CT use have increased awareness in the medical community and efforts have been made to ensure that diagnostic procedures involving ionising radiation are performed only if absolutely necessary for a patient's care (justified) and to provide images adequate for diagnosis while keeping the radiation dose levels as low as reasonably achievable (optimisation). These principles are notably enforced for paediatric patients.

## 3. Scientific justification of the recommendation

In summary, current evidence shows that HRT is associated with an increased risk of cancers of the breast, endometrium, and ovary [3]. The risk pattern depends on the type of therapy (oestrogen-only or combined oestrogen–progestogen), initiation according to time of menopause, and whether the woman has undergone hysterectomy. The European Code against Cancer recommends limiting or avoiding, when possible, the use of HRT, i.e. mainly menopausal hormone therapy, due to the increased cancer risk. Women with severe menopausal symptoms may discuss with their physician whether to use HRT; however, it should not be used for purposes of disease prevention. The therapeutic approach should be discussed thoroughly with the physician before treatment is started. The individual clinician is obligated to inform women on the risks and benefits of HRT to ensure that patients make informed, individualised decisions. In general, menopausal hormone treatment should employ the lowest dose for the shortest period possible. More research is needed on HRT to clarify the implications related to cancer risk.

Ionising radiation is an established carcinogen, and medical applications of radiation for diagnosis and treatment are major sources of radiation exposure for the European population. Application of medical radiation can provide major health benefits, but due to the potential increase in cancer risk, prudent practises ensuring justification in terms of benefits and harms are required, with procedures and techniques providing the needed diagnostic information or therapeutic gain with the least possible radiation exposure.

## 4. Conclusions

Principles of the 4th revision of the European Code against Cancer were that the recommendations are (1) based on sufficient scientific evidence of carcinogenicity, (2) suitable for a broad target group, (3) something individuals can do to reduce their cancer risk, and (4) that the recommendations can be clearly communicated to the general population [1]. All four principles were judged to be fulfilled for HRT, although HRT has a certain therapeutic potential after thorough benefit–risk evaluation by physicians. For other medical exposures, the established carcinogenic effects were not conceived to be clearly communicable to the general population, exemplified by diagnostic X-ray which poses undue risk if used unnecessarily, but also cause an important health risk if a necessary examination is avoided because of fear of radiation.

Other drugs with established carcinogenic effects in humans include anti-neoplastic agents used in cancer therapy, immunosuppressants, oestrogen–progestogen contraceptives, and tamoxifen. Prescription of carcinogenic drugs for cancer-free individuals should be based on careful benefit–risk considerations and the available evidence [3,5]. Targeted treatments with tamoxifen, aromatase inhibitors and immunosuppressants are typically endorsed from a clinical perspective. In contrast, hormonal contraceptives cannot be recommended alone from a cancer perspective, since these agents possesses both cancer preventive and carcinogenic effects. Because oral contraceptives are prescribed for healthy individuals, any decision to use these drugs should be based on a thorough evaluation of the risk–benefit profile of each individual woman. Irrespective of drug type, long-term monitoring of potential carcinogenic risk is imperative. No straightforward recommendation can be given to the general population.

Although a large number of chemopreventive agents have been investigated, to date none has been found to be clinically useful, except within selected, high-risk groups. Therefore, further research is required to find chemopreventive agents that are

effective, safe, and tolerable. Chemoprevention cannot be recommended for the healthy population, but these agents provide a potential therapeutic option for individuals at high risk of developing cancer. Any chemopreventive approach should be started only after consulting a physician who can supervise the treatment. Self-medication with aspirin or other potential chemopreventive drugs is strongly discouraged, due to the possibility of serious, potentially lethal, adverse events.

Radiation therapy is established to cause an increased risk of second primary cancer; however, the absolute excess is small, and the benefits of radiation therapy virtually always outweigh the risks. Similarly, high-dose diagnostic procedures, such as CT, are associated with a small cancer risk, but the immediate benefits of CT generally outweigh the long-term risks, if used diligently. Clinicians face the task of making decisions about the benefit to the patient in relation to the small excess cancer risk associated with radiation exposure; however, existing guidelines and recommendations are helpful in this decision-making. Therefore, although the diagnostic procedures involving ionising radiation increase the risk of cancer development, the vast majority of examinations are medically justified and provide overall benefit to the patients. No recommendation can be given to the general population, as healthcare professionals represent the target group for continuously updated information of carcinogenic effects of radiation, and avoidance of unnecessary use.

## Conflict of interest

Søren Friis has participated in a research project requested by the European Medicines Agency (EMA) and funded by Lundbeck A/S with grants paid to the Danish Cancer Society Research Center. The funding source (Lundbeck) had no role in the design, conduct, analysis, interpretation or reporting of the study. The other authors declare no conflict of interest.

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## References

[1] J. Schüz, C. Espina, P. Villain, R. Herrero, M.E. Leon, S. Minozzi, et al., European Code against Cancer 4th Edition: 12 ways to reduce your cancer risk. Cancer Epidemiol 39 (2015) S1–S10.
[2] International Agency for Research on Cancer, IARC monographs on the evaluation of carcinogenic risks to humans. Combined Estrogen–Progestogen Contraceptives and Combined Estrogen–Progestogen Menopausal therapy, vol. 91, WHO, Lyon, France, 2007.
[3] International Agency for Research on Cancer, IARC monographs on the evaluation of carcinogenic risks to humans. A Review of Human Carcinogens, Part A: Pharmaceuticals, vol. 100A, WHO, Lyon, France, 2012.
[4] F.E. Vera-Badillo, M. Al-Mubarak, A.J. Templeton, E. Amir, Benefit and harms of new anti-cancer drugs. Curr. Oncol. Rep. 15 (3) (2013) 270–275.
[5] A. Jacobs, D. Jacobson-Kram, Human carcinogenic risk evaluation, Part III. Assessing cancer hazard and risk in human drug development. Toxicol. Sci. 81 (2) (2004) 260–262.
[6] H.B. Peterson, S.B. Thacker, P.S. Corso, P.A. Marchbanks, J.P. Koplan, Hormone therapy: making decisions in the face of uncertainty. Arch. Intern. Med. 164 (21) (2004) 2308–2312.
[7] H.J. Burstein, A.A. Prestrud, J. Seidenfeld, H. Anderson, T.A. Buchholz, N.E. Davidson, et al., American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J. Clin. Oncol. 28 (23) (2010) 3784–3796.
[8] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation. Cell 144 (5) (2011) 646–674.
[9] A. Umar, B.K. Dunn, P. Greenwald, Future directions in cancer prevention. Nat. Rev. Cancer 12 (12) (2012) 835–848.
[10] N. Saijo, T. Tamura, K. Nishio, Strategy for the development of novel anticancer drugs. Cancer Chemother. Pharmacol. 52 (Suppl. (1)) (2003) 97–101.
[11] G.J. Kelloff, S.M. Lippman, A.J. Dannenberg, C.C. Sigman, H.L. Pearce, B.J. Reid, et al., Progress in chemoprevention drug development: the promise of molecular biomarkers for prevention of intraepithelial neoplasia and cancer—a plan to move forward. Clin. Cancer Res. 12 (12) (2006) 3661–3697.
[12] N. McColl, A. Auvinen, A. Kesminiene, C. Espina, F. Erdmann, E. de Vries, et al., European Code against Cancer 4th Edition: ionising and non-ionising radiation and cancer. Cancer Epidemiol 39 (2015) S93–S100.
[13] Royal College of Radiologists, Making the Best Use of a Department of Clinical Radiology. 4th ed., Royal College of Radiologists, London, 1998.
[14] V.J. Cogliano, R. Baan, K. Straif, Y. Grosse, B. Lauby-Secretan, F. El Ghissassi, et al., Preventable exposures associated with human cancers. J. Natl. Cancer Inst. 103 (24) (2011) 1827–1839.
[15] C. Lauritzen, J. Studd, Current Management of the Menopause. Taylor & Francis, Oxon, UK, 2005.
[16] M.L. Stefanick, Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. Am. J. Med. 118 (Suppl. (12B)) (2005) 64–73.
[17] Brayfield A. Martindale, The Complete Drug Reference. 38th ed., Pharmaceutical Press, Royal Pharmaceutical Society, London, 2014.
[18] M.I. Whitehead, S. Campbell, G. Dyer, W.P. Collins, J. Pryse-Davies, T.A. Ryder, et al., Progestogen modification of endometrial histology in menopasual women. Br. Med. J. 2 (6152) (1978) 1643–1644.
[19] Collaborative Group on Hormonal Factors in Breast Cancer, Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 350 (9084) (1997) 1047–1059.
[20] R.A. Lobo, Benefits and risks of estrogen replacement therapy. Am. J. Obstet. Gynecol. 173 (3 Pt. 2) (1995) 982–989.
[21] J.E. Rossouw, G.L. Anderson, R.L. Prentice, A.Z. Lacroix, C. Kooperberg, M.L. Stefanick, et al., Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 288 (3) (2002) 321–333.
[22] J.E. Manson, J. Hsia, K.C. Johnson, J.E. Rossouw, A.R. Assaf, N.L. Lasser, et al., Estrogen plus progestin and the risk of coronary heart disease. N. Engl. J. Med. 349 (6) (2003) 523–534.
[23] H.N. Hodis, W.J. Mack, R. Lobo, Postmenopausal hormone replacement therapy as antiatherosclerotic therapy. Curr. Atheroscler Rep. 4 (1) (2002) 52–58.
[24] G.L. Anderson, M. Limacher, A.R. Assaf, T. Bassford, S.A. Beresford, H. Black, et al., Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 291 (14) (2004) 1701–1712.
[25] P.M. Ravdin, K.A. Cronin, N. Howlader, C.D. Berg, R.T. Chlebowski, E.J. Feuer, et al., The decrease in breast cancer incidence in 2003 in the United States. N. Engl. J. Med. 356 (16) (2007) 1670–1674.
[26] A. Katalinic, R. Rawal, Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy. Breast Cancer Res. Treat. 107 (3) (2008) 427–430.
[27] C. Bouchardy, A. Morabia, H.M. Verkooijen, G. Fioretta, Y. Wespi, P. Schafer, Remarkable change in age-specific breast cancer incidence in the Swiss canton of Geneva and its possible relation with the use of hormone replacement therapy. BMC Cancer 6 (2006) 78.
[28] R.T. Chlebowski, L.H. Kuller, R.L. Prentice, M.L. Stefanick, J.E. Manson, M. Gass, et al., Breast cancer after use of estrogen plus progestin in postmenopausal women. N. Engl. J. Med. 360 (6) (2009) 573–587.
[29] S.F. Marshall, C.A. Clarke, D. Deapen, K. Henderson, J. Largent, S.L. Neuhausen, et al., Recent breast cancer incidence trends according to hormone therapy use: the California Teachers Study cohort. Breast Cancer Res. 12 (1) (2010) R4.
[30] E. Banks, K. Canfell, Recent declines in breast cancer incidence: mounting evidence that reduced use of menopausal hormones is largely responsible. Breast Cancer Res. 12 (1) (2010) 103.
[31] C. Antoine, L. Ameye, M. Paesmans, S. Rozenberg, Systematic review about breast cancer incidence in relation to hormone replacement therapy use. Climacteric 17 (2) (2014) 116–132.
[32] A. Gompel, S. Rozenberg, D.H. Barlow, The EMAS 2008 update on clinical recommendations on postmenopausal hormone replacement therapy. Maturitas 61 (3) (2008) 227–232.
[33] D.W. Sturdee, A. Pines, D.F. Archer, R.J. Baber, D. Barlow, M.H. Birkhauser, et al., Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. Climacteric 14 (3) (2011) 302–320.
[34] H.D. Nelson, M. Walker, B. Zakher, J. Mitchell, Menopausal hormone therapy for the primary prevention of chronic conditions: a systematic review to update the U.S. Preventive Services Task Force recommendations. Ann. Intern. Med. 157 (2) (2012) 104–113.
[35] V.A. Moyer, Menopausal hormone therapy for the primary prevention of chronic conditions: U.S. Preventive Services Task Force recommendation statement. Ann. Intern. Med. 158 (1) (2013) 47–54.
[36] A.Z. Lacroix, R.T. Chlebowski, J.E. Manson, A.K. Aragaki, K.C. Johnson, L. Martin, et al., Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA 305 (13) (2011) 1305–1314.

[37] L.L. Schierbeck, L. Rejnmark, C.L. Tofteng, L. Stilgren, P. Eiken, L. Mosekilde, et al., Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ 345 (2012) e6409.
[38] H.M. Boardman, L. Hartley, A. Eisinga, C. Main, M. Roqué i Figuls, X. Bonfill Cosp, et al., Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst. Rev. 3 (2015) CD002229.
[39] Million Women Study Collaborators, V. Beral, Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 362 (9382) (2003) 419–427.
[40] J.A. Collins, J.M. Blake, P.G. Crosignani, Breast cancer risk with postmenopausal hormonal treatment. Hum. Reprod. Update 11 (6) (2005) 545–560.
[41] C.M. Greiser, E.M. Greiser, M. Doren, Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials. Hum. Reprod. Update 11 (6) (2005) 561–573.
[42] K. Bakken, A. Fournier, E. Lund, M. Waaseth, V. Dumeaux, F. Clavel-Chapelon, et al., Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. Int. J. Cancer 128 (1) (2011) 144–156.
[43] V. Beral, G. Reeves, D. Bull, J. Green, Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J. Natl. Cancer Inst. 103 (4) (2011) 296–305.
[44] R.T. Chlebowski, J.E. Manson, G.L. Anderson, J.A. Cauley, A.K. Aragaki, M.L. Stefanick, et al., Estrogen plus progestin and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. J. Natl. Cancer Inst. 105 (8) (2013) 526–535.
[45] G.L. Anderson, R.T. Chlebowski, A.K. Aragaki, L.H. Kuller, J.E. Manson, M. Gass, et al., Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol. 13 (5) (2012) 476–486.
[46] R.L. Prentice, R.T. Chlebowski, M.L. Stefanick, J.E. Manson, R.D. Langer, M. Pettinger, et al., Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. Am. J. Epidemiol. 167 (12) (2008) 1407–1415.
[47] R.T. Chlebowski, G.L. Anderson, Menopausal hormone therapy and breast cancer mortality: clinical implications. Ther. Adv. Drug Saf. 6 (2) (2015) 45–56.
[48] G.L. Anderson, R.T. Chlebowski, A.K. Aragaki, L.H. Kuller, J.E. Manson, M. Gass, et al., Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol. 13 (5) (2012) 476–486.
[49] A. Fournier, S. Mesrine, M.C. Boutron-Ruault, F. Clavel-Chapelon, Estrogen-progestagen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? J. Clin. Oncol. 27 (31) (2009) 5138–5143.
[50] G.K. Reeves, V. Beral, J. Green, T. Gathani, D. Bull, Hormonal therapy for menopause and breast cancer risk by histological type: a cohort study and meta-analysis. Lancet Oncol. 7 (11) (2006) 910–918.
[51] R.L. Prentice, R.T. Chlebowski, M.L. Stefanick, J.E. Manson, M. Pettinger, S.L. Hendrix, et al., Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. Am. J. Epidemiol. 167 (10) (2008) 1207–1216.
[52] C.J. Crandall, A.K. Aragaki, J.A. Cauley, A. McTiernan, J.E. Manson, G. Anderson, R.T. Chlebowski, Breast tenderness and breast cancer risk in the estrogen plus progestin and estrogen-alone women's health initiative clinical trials. Breast Cancer Res. Treat. 132 (1) (2012) 275–285.
[53] N. Hou, S. Hong, W. Wang, O.I. Olopade, J.J. Dignam, D. Huo, Hormone replacement therapy and breast cancer: heterogeneous risks by race, weight, and breast density. J. Natl. Cancer Inst. 105 (18) (2013) 1365–1372.
[54] S.A. Narod, Hormone replacement therapy and the risk of breast cancer. Nat. Rev. Clin. Oncol. 8 (11) (2011) 669–676.
[55] R.J. Santen, Menopausal hormone therapy and breast cancer. J. Steroid Biochem. Mol. Biol. 142 (2014) 52–61.
[56] R.T. Chlebowski, G.L. Anderson, The influence of time from menopause and mammography on hormone therapy-related breast cancer risk assessment. J. Natl. Cancer Inst. 103 (4) (2011) 284–285.
[57] A. Fournier, F. Berrino, E. Riboli, V. Avenel, F. Clavel-Chapelon, Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. Int. J. Cancer 114 (3) (2005) 448–454.
[58] M. Ewertz, L. Mellemkjaer, A.H. Poulsen, S. Friis, H.T. Sorensen, L. Pedersen, et al., Hormone use for menopausal symptoms and risk of breast cancer. A Danish cohort study. Br. J. Cancer 92 (7) (2005) 1293–1297.
[59] B. Pesch, Y. Ko, H. Brauch, U. Hamann, V. Harth, S. Rabstein, et al., Factors modifying the association between hormone-replacement therapy and breast cancer risk. Eur. J. Epidemiol. 20 (8) (2005) 699–711.
[60] R.T. Chlebowski, G.L. Anderson, M. Gass, D.S. Lane, A.K. Aragaki, L.H. Kuller, et al., Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA 304 (15) (2010) 1684–1692.
[61] K.K. Tsilidis, N.E. Allen, T.J. Key, L. Dossus, R. Kaaks, K. Bakken, et al., Menopausal hormone therapy and risk of ovarian cancer in the European prospective investigation into cancer and nutrition. Cancer Causes Control 22 (8) (2011) 1075–1084.
[62] J.E. Manson, R.T. Chlebowski, M.L. Stefanick, A.K. Aragaki, J.E. Rossouw, R.L. Prentice, et al., Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 310 (13) (2013) 1353–1368.
[63] S. Furness, H. Roberts, J. Marjoribanks, A. Lethaby, Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst. Rev. 8 (2012) CD000402.
[64] D. Grady, T. Gebretsadik, K. Kerlikowske, V. Ernster, D. Petitti, Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet. Gynecol. 85 (2) (1995) 304–313.
[65] V. Beral, D. Bull, G. Reeves, Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet 365 (9470) (2005) 1543–1551.
[66] N.E. Allen, K.K. Tsilidis, T.J. Key, L. Dossus, R. Kaaks, E. Lund, et al., Menopausal hormone therapy and risk of endometrial carcinoma among postmenopausal women in the European Prospective Investigation Into Cancer and Nutrition. Am. J. Epidemiol. 172 (12) (2010) 1394–1403.
[67] A.I. Phipps, J.A. Doherty, L.F. Voigt, D.A. Hill, S.A. Beresford, M.A. Rossing, et al., Long-term use of continuous-combined estrogen-progestin hormone therapy and risk of endometrial cancer. Cancer Causes Control 22 (12) (2011) 1639–1646.
[68] B. Trabert, N. Wentzensen, H.P. Yang, M.E. Sherman, A.R. Hollenbeck, Y. Park, L.A. Brinton, Is estrogen plus progestin menopausal hormone therapy safe with respect to endometrial cancer risk? Int. J. Cancer 132 (2) (2013) 417–426.
[69] L.A. Brinton, A.S. Felix, Menopausal hormone therapy and risk of endometrial cancer. J. Steroid Biochem. Mol. Biol. 142 (2014) 83–89.
[70] C.L. Pearce, K. Chung, M.C. Pike, A.H. Wu, Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin. Cancer 115 (3) (2009) 531–539.
[71] K.K. Tsilidis, N.E. Allen, T.J. Key, L. Dossus, R. Kaaks, K. Bakken, et al., Menopausal hormone therapy and risk of ovarian cancer in the European prospective investigation into cancer and nutrition. Cancer Causes Control 22 (8) (2011) 1075–1084.
[72] L.S. Mørch, E. Løkkegaard, A.H. Andreasen, S.K. Kjær, O. Lidegaard, Hormone therapy and different ovarian cancers: a national cohort study. Am. J. Epidemiol. 175 (12) (2012) 1234–1242.
[73] V. Beral, K. Gaitskell, C. Hermon, K. Moser, G. Reeves, R. Peto, the Collaborative Group on Epidemiological Studies of Ovarian Cancer, Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet 385 (9980) (2015) 1835–1842.
[74] V. Beral, D. Bull, J. Green, G. Reeves, Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet 369 (9574) (2007) 1703–1710.
[75] A. Gompel, H. Burger, A Commentary on a recent update of the ovarian cancer risk attributable to menopausal hormone therapy. Climacteric 18 (3) (2015) 376–378.
[76] F. Grodstein, P.A. Newcomb, M.J. Stampfer, Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am. J. Med. 106 (5) (1999) 574–582.
[77] K. Nanda, L.A. Bastian, V. Hasselblad, D.L. Simel, Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. Obstet. Gynecol. 93 (5 Pt. 2) (1999) 880–888.
[78] E.L. Barnes, M.D. Long, Colorectal cancer in women: hormone replacement therapy and chemoprevention. Climacteric 15 (3) (2012) 250–255.
[79] K.J. Lin, W.Y. Cheung, J.Y. Lai, E.L. Giovannucci, The effect of estrogen vs. combined estrogen-progestogen therapy on the risk of colorectal cancer. Int. J. Cancer 130 (2) (2012) 419–430.
[80] J. Green, G. Czanner, G. Reeves, J. Watson, L. Wise, A. Roddam, V. Beral, Menopausal hormone therapy and risk of gastrointestinal cancer: nested case-control study within a prospective cohort, and meta-analysis. Int. J. Cancer 130 (10) (2012) 2387–2396.
[81] C.M. Johnson, C. Wei, J.E. Ensor, D.J. Smolenski, C.I. Amos, B. Levin, D.A. Berry, Meta-analyses of colorectal cancer risk factors. Cancer Causes Control 24 (6) (2013) 1207–1222.
[82] M. Wahab, F. Al-Azzawi, Meningioma and hormonal influences. Climacteric 6 (4) (2003) 285–292.
[83] S. Blitshteyn, J.E. Crook, K.A. Jaeckle, Is there an association between meningioma and hormone replacement therapy? J. Clin. Oncol. 26 (2) (2008) 279–282.
[84] V.S. Benson, K. Pirie, J. Green, D. Bull, D. Casabonne, G.K. Reeves, V. Beral, Hormone replacement therapy and incidence of central nervous system tumours in the Million Women Study. Int. J. Cancer 127 (7) (2010) 1692–1698.
[85] L. Andersen, S. Friis, J. Hallas, P. Ravn, H.D. Schroder, D. Gaist, Hormone replacement therapy increases the risk of cranial meningioma. Eur. J. Cancer 49 (15) (2013) 3303–3310.
[86] Z.X. Fan, J. Shen, Y.Y. Wu, H. Yu, Y. Zhu, R.Y. Zhan, Hormone replacement therapy and risk of meningioma in women: a meta-analysis. Cancer Causes Control 24 (8) (2013) 1517–1525.
[87] M.C. Camargo, Y. Goto, J. Zabaleta, D.R. Morgan, P. Correa, C.S. Rabkin, Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. Cancer Epidemiol. Biomarkers Prev. 21 (1) (2012) 20–38.
[88] K. Lagergren, J. Lagergren, N. Brusselaers, Hormone replacement therapy and oral contraceptives and risk of oesophageal adenocarcinoma: a systematic review and meta-analysis. Int. J. Cancer 135 (9) (2014) 2183–2190.
[89] Y. Yao, X. Gu, J. Zhu, D. Yuan, Y. Song, Hormone replacement therapy in females can decrease the risk of lung cancer: a meta-analysis. PLoS One 8 (8) (2013) e71236.
[90] R.T. Chlebowski, G.L. Anderson, J.E. Manson, A.G. Schwartz, H. Wakelee, M. Gass, et al., Lung cancer among postmenopausal women treated with

estrogen alone in the women's health initiative randomized trial. J. Natl. Cancer Inst. 102 (18) (2010) 1413–1421.
[91] R.T. Chlebowski, A.G. Schwartz, H. Wakelee, G.L. Anderson, M.L. Stefanick, J.E. Manson, et al., Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. Lancet 374 (9697) (2009) 1243–1251.
[92] K. Grindlay, B. Burns, D. Grossman, Prescription requirements and over-the-counter access to oral contraceptives: a global review. Contraception 88 (1) (2013) 91–96.
[93] WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC Classification and DDD Assignment. WHO, Oslo, 2013.
[94] A.L. Spencer, R. Bonnema, M.C. McNamara, Helping women choose appropriate hormonal contraception: update on risks, benefits, and indications. Am. J. Med. 122 (6) (2009) 497–506.
[95] B.E. McKenzie, Guidelines and requirements for the evaluation of contraceptive steroids. Toxicol. Pathol. 17 (2) (1989) 377–384.
[96] D. Cibula, A. Gompel, A.O. Mueck, C. La Vecchia, P.C. Hannaford, S.O. Skouby, et al., Hormonal contraception and risk of cancer. Hum. Reprod. Update 16 (6) (2010) 631–650.
[97] A.C. Jacobs, K.P. Hatfield, History of chronic toxicity and animal carcinogenicity studies for pharmaceuticals. Vet. Pathol. 50 (2) (2013) 324–333.
[98] Collaborative Group on Hormonal Factors in Breast Cancer, Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet 347 (9017) (1996) 1713–1727.
[99] C. Kahlenborn, F. Modugno, D.M. Potter, W.B. Severs, Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis. Mayo Clin. Proc. 81 (10) (2006) 1290–1302.
[100] H. Zhu, X. Lei, J. Feng, Y. Wang, Oral contraceptive use and risk of breast cancer: a meta-analysis of prospective cohort studies. Eur. J. Contracept. Reprod. Health Care 17 (6) (2012) 402–414.
[101] P. Appleby, V. Beral, A. Berrington de González, D. Colin, S. Franceschi, A. Goodhill, et al., Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. Lancet 370 (9599) (2007) 1609–1621.
[102] S. Maheshwari, A. Sarraj, J. Kramer, H.B. El-Serag, Oral contraception and the risk of hepatocellular carcinoma. J. Hepatol. 47 (4) (2007) 506–513.
[103] B.H. Stegeman, M. de Bastos, F.R. Rosendaal, A. van Hylckama Vlieg, F.M. Helmerhorst, T. Stijnen, O.M. Dekkers, Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. BMJ 347 (2013) f5298.
[104] L.J. Havrilesky, P.G. Moorman, W.J. Lowery, J.M. Gierisch, R.R. Coeytaux, R.P. Urrutia, et al., Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstet. Gynecol. 122 (1) (2013) 139–147.
[105] A.O. Mueck, H. Seeger, T. Rabe, Hormonal contraception and risk of endometrial cancer: a systematic review. Endocr. Relat. Cancer 17 (4) (2010) R263–R271.
[106] D.A. Grimes, K.E. Economy, Primary prevention of gynecologic cancers. Am. J. Obstet. Gynecol. 172 (1 Pt. 1) (1995) 227–235.
[107] J.J. Schlesselman, Risk of endometrial cancer in relation to use of combined oral contraceptives. A practitioner's guide to meta-analysis. Hum. Reprod. 12 (9) (1997) 1851–1863.
[108] E. Fernandez, C. La Vecchia, A. Balducci, L. Chatenoud, S. Franceschi, E. Negri, Oral contraceptives and colorectal cancer risk: a meta-analysis. Br. J. Cancer 84 (5) (2001) 722–727.
[109] M.R. Karagas, T.A. Stukel, J. Dykes, J. Miglionico, M.A. Greene, M. Carey, et al., A pooled analysis of 10 case-control studies of melanoma and oral contraceptive use. Br. J. Cancer 86 (7) (2002) 1085–1092.
[110] J.S. Smith, J. Green, A. Berrington de González, P. Appleby, J. Peto, M. Plummer, et al., Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet 361 (9364) (2003) 1159–1167.
[111] C. Bosetti, F. Bravi, E. Negri, C. La Vecchia, Oral contraceptives and colorectal cancer risk: a systematic review and meta-analysis. Hum. Reprod. Update 15 (5) (2009) 489–498.
[112] S. Iodice, M. Barile, N. Rotmensz, I. Feroce, B. Bonanni, P. Radice, et al., Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur. J. Cancer 46 (12) (2010) 2275–2284.
[113] W. Blonski, D.S. Kotlyar, K.A. Forde, Non-viral causes of hepatocellular carcinoma. World J. Gastroenterol. 16 (29) (2010) 3603–3615.
[114] D. Cibula, M. Zikan, L. Dusek, O. Majek, Oral contraceptives and risk of ovarian and breast cancers in BRCA mutation carriers: a meta-analysis. Expert Rev. Anticancer Ther. 11 (8) (2011) 1197–1207.
[115] S. Gandini, S. Iodice, E. Koomen, A. Di Pietro, F. Sera, S. Caini, Hormonal and reproductive factors in relation to melanoma in women: current review and meta-analysis. Eur. J. Cancer 47 (17) (2011) 2607–2617.
[116] E.V. Kane, E. Roman, N. Becker, L. Bernstein, P. Boffetta, P.M. Bracci, et al., Menstrual and reproductive factors, and hormonal contraception use: associations with non-Hodgkin lymphoma in a pooled analysis of InterLymph case-control studies. Ann. Oncol. 23 (9) (2012) 2362–2374.
[117] P.G. Moorman, L.J. Havrilesky, J.M. Gierisch, R.R. Coeytaux, W.J. Lowery, U.R. Peragallo, et al., Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J. Clin. Oncol. 31 (33) (2013) 4188–4198.
[118] J.M. Gierisch, R.R. Coeytaux, R.P. Urrutia, L.J. Havrilesky, P.G. Moorman, W.J. Lowery, et al., Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol. Biomarkers Prev. 22 (11) (2013) 1931–1943.
[119] W. Wu, Z.H. Yin, P. Guan, Y.W. Ren, B.S. Zhou, Association of oral contraceptives use and lung cancer risk among women: an updated meta-analysis based on cohort and case-control studies. Asian Pac. J. Cancer Prev. 15 (3) (2014) 1205–1210.
[120] H. Liu, X.C. Wang, G.H. Hu, T.B. Huang, Y.F. Xu, Oral contraceptive use and kidney cancer risk among women: evidence from a meta-analysis. Int. J. Clin. Exp. Med. 7 (11) (2014) 3954–3963.
[121] J. Cuzick, A. DeCensi, B. Arun, P.H. Brown, M. Castiglione, B. Dunn, et al., Preventive therapy for breast cancer: a consensus statement. Lancet Oncol. 12 (5) (2011) 496–503.
[122] H.D. Nelson, M.E. Smith, J.C. Griffin, R. Fu, Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann. Intern. Med. 158 (8) (2013) 604–614.
[123] J.H. Olsen, T. Møller, H. Anderson, F. Langmark, R. Sankila, L. Tryggvadottir, et al., Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. J. Natl. Cancer Inst. 101 (11) (2009) 806–813.
[124] L.B. Travis, W.W. Demark, J.M. Allan, M.E. Wood, A.K. Ng, Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. Nat. Rev. Clin. Oncol. 10 (5) (2013) 289–301.
[125] M.E. Wood, V. Vogel, A. Ng, L. Foxhall, P. Goodwin, L.B. Travis, Second malignant neoplasms: assessment and strategies for risk reduction. J. Clin. Oncol. 30 (30) (2012) 3734–3745.
[126] Y. Grosse, R. Baan, K. Straif, B. Secretan, F. El Ghissassi, V. Bouvard, et al., A review of human carcinogens-Part A: pharmaceuticals. Lancet Oncol. 10 (1) (2009) 13–14.
[127] L.A. Godley, R.A. Larson, Therapy-related myeloid leukemia. Semin. Oncol. 35 (4) (2008) 418–429.
[128] H. Sill, W. Olipitz, A. Zebisch, E. Schulz, A. Wolfler, Therapy-related myeloid neoplasms: pathobiology and clinical characteristics. Br. J. Pharmacol. 162 (4) (2011) 792–805.
[129] P. Vineis, R. Pirastu, Aromatic amines and cancer. Cancer Causes Control 8 (3) (1997) 346–355.
[130] A.J. Swerdlow, C.D. Higgins, P. Smith, D. Cunningham, B.W. Hancock, A. Horwich, et al., Second cancer risk after chemotherapy for Hodgkin's lymphoma: a collaborative British cohort study. J. Clin. Oncol. 29 (31) (2011) 4096–4104.
[131] L.B. Travis, W.W. Demark, J.M. Allan, M.E. Wood, A.K. Ng, Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. Nat. Rev. Clin. Oncol. 10 (5) (2013) 289–301.
[132] J.S. Maltzman, G.A. Koretzky, Azathioprine old drug, new actions. J. Clin. Invest. 111 (8) (2003) 1122–1124.
[133] P. Forsythe, S. Paterson, Ciclosporin 10 years on: indications and efficacy. Vet. Rec. 174 (Suppl. (2)) (2014) 13–21.
[134] I. Rama, J.M. Grinyo, Malignancy after renal transplantation: the role of immunosuppression. Nat. Rev. Nephrol. 6 (9) (2010) 511–519.
[135] A. Corthay, Does the immune system naturally protect against cancer? Front. Immunol. 5 (2014) 197.
[136] S. Euvrard, J. Kanitakis, A. Claudy, Skin cancers after organ transplantation. N. Engl. J. Med. 348 (17) (2003) 1681–1691.
[137] A. Gutierrez-Dalmau, J.M. Campistol, Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. Drugs 67 (8) (2007) 1167–1198.
[138] E.A. Engels, R.M. Pfeiffer, J.F. Fraumeni Jr., B.L. Kasiske, A.K. Israni, J.J. Snyder, et al., Spectrum of cancer risk among US solid organ transplant recipients. JAMA 306 (17) (2011) 1891–1901.
[139] H.H. Schmeiser, J.E. Kucab, V.M. Arlt, D.H. Phillips, M. Hollstein, G. Gluhovschi, et al., Evidence of exposure to aristolochic acid in patients with urothelial cancer from a Balkan endemic nephropathy region of Romania. Environ. Mol. Mutagen 53 (8) (2012) 636–641.
[140] C.H. Chen, K.G. Dickman, M. Moriya, J. Zavadil, V.S. Sidorenko, K.L.J.T. Edwards, et al., Aristolochic acid-associated urothelial cancer in Taiwan. Proc. Natl. Acad. Sci. U. S. A. 109 (21) (2012) 8241–8246.
[141] H.H. Schmeiser, M. Stiborova, V.M. Arlt, Chemical and molecular basis of the carcinogenicity of Aristolochia plants. Curr. Opin. Drug Discov. Dev. 12 (1) (2009) 141–148.
[142] M. Hollstein, M. Moriya, A.P. Grollman, M. Olivier, Analysis of TP53 mutation spectra reveals the fingerprint of the potent environmental carcinogen, aristolochic acid. Mutat. Res. 753 (1) (2013) 41–49.
[143] D. Krell, J. Stebbing, Aristolochia the malignant truth. Lancet Oncol. 14 (1) (2013) 25–26.
[144] W. McNeely, K.L. Goa, 5-Methoxypsoralen. A review of its effects in psoriasis and vitiligo. Drugs 56 (4) (1998) 667–690.
[145] E. Archier, S. Devaux, E. Castela, A. Gallini, F. Aubin, M.M. Le, et al., Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. J. Eur. Acad. Dermatol. Venereol. 26 (Suppl. (3)) (2012) 22–31.
[146] G.D. Friedman, M.M. Asgari, E.M. Warton, J. Chan, L.A. Habel, Antihypertensive drugs and lip cancer in non-Hispanic whites. Arch. Intern. Med. 172 (16) (2012) 1246–1251.
[147] M.B. Sporn, N.M. Dunlop, D.L. Newton, J.M. Smith, Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). Fed. Proc. 35 (6) (1976) 1332–1338.

[148] S.L. Patterson, M.K. Colbert, E. Hawk, Cancer chemoprevention: successes and failures. Clin. Chem. 59 (1) (2013) 94–101.
[149] J.V. Pinkerton, S. Thomas, Use of SERMs for treatment in postmenopausal women. J. Steroid Biochem. Mol. Biol. 142C (2014) 142–154.
[150] R. Sainsbury, The development of endocrine therapy for women with breast cancer. Cancer Treat. Rev. 39 (5) (2013) 507–517.
[151] K. Visvanathan, P. Hurley, E. Bantug, P. Brown, N.F. Col, J. Cuzick, et al., Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. J. Clin. Oncol. 31 (23) (2013) 2942–2962.
[152] J. Cuzick, I. Sestak, B. Bonanni, J.P. Costantino, S. Cummings, A. DeCensi, et al., Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet 381 (9880) (2013) 1827–1834.
[153] P.E. Goss, J.N. Ingle, J.E. Ales-Martinez, A.M. Cheung, R.T. Chlebowski, J. Wactawski-Wende, et al., Exemestane for breast-cancer prevention in postmenopausal women. N. Engl. J. Med. 364 (25) (2011) 2381–2391.
[154] J. Cuzick, I. Sestak, J.F. Forbes, M. Dowsett, J. Knox, S. Cawthorn, et al., Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 383 (9922) (2014) 1041–1048.
[155] J. Cuzick, F. Otto, J.A. Baron, P.H. Brown, J. Burn, P. Greenwald, et al., Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol. 10 (5) (2009) 501–507.
[156] A.T. Chan, N. Arber, J. Burn, W.K. Chia, P. Elwood, M.A. Hull, et al., Aspirin in the chemoprevention of colorectal neoplasia: an overview. Cancer Prev. Res. (Phila) 5 (2) (2012) 164–178.
[157] S. Friis, A.H. Riis, R. Erichsen, J.A. Baron, H.T. Sørensen, Low-dose aspirin or nonsteroidal anti-inflammatory drug use and colorectal cancer risk: A population-based, case-control study. Ann. Intern. Med. 163 (5) (2015) 347–355.
[158] J. Cuzick, M.A. Thorat, C. Bosetti, P.H. Brown, J. Burn, N.R. Cook, et al., Estimates of benefits and harms of prophylactic use of aspirin in the general population. Ann. Oncol. 1 (2015) 47–57.
[159] N.R. Cook, I.M. Lee, S.M. Zhang, M.V. Moorthy, J.E. Buring, Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. Ann. Intern. Med. 159 (2) (2013) 77–85.
[160] P.M. Rothwell, M. Wilson, C.E. Elwin, B. Norrving, A. Algra, C.P. Warlow, T.W. Meade, Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 376 (9754) (2010) 1741–1750.
[161] P.M. Rothwell, J.F. Price, F.G. Fowkes, A. Zanchetti, M.C. Roncaglioni, G. Tognoni, et al., Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 379 (9826) (2012) 1602–1612.
[162] J.A. Baron, R.S. Sandler, R.S. Bresalier, H. Quan, R. Riddell, A. Lanas, et al., A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology 131 (6) (2006) 1674–1682.
[163] M.M. Bertagnolli, C.J. Eagle, A.G. Zauber, M. Redston, S.D. Solomon, K. Kim, et al., Celecoxib for the prevention of sporadic colorectal adenomas. N. Engl. J. Med. 355 (9) (2006) 873–884.
[164] N. Arber, C.J. Eagle, J. Spicak, I. Racz, P. Dite, J. Hajer, et al., Celecoxib for the prevention of colorectal adenomatous polyps. N. Engl. J. Med. 355 (9) (2006) 885–895.
[165] B.F. Cole, R.F. Logan, S. Halabi, R. Benamouzig, R.S. Sandler, M.J. Grainge, et al., Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. J. Natl. Cancer Inst. 101 (4) (2009) 256–266.
[166] H. Ishikawa, M. Mutoh, S. Suzuki, S. Tokudome, Y. Saida, T. Abe, et al., The preventive effects of low-dose enteric-coated aspirin tablets on the development of colorectal tumours in Asian patients: a randomised trial. Gut 63 (11) (2014) 1755–1759.
[167] K.P. Nugent, K.C. Farmer, A.D. Spigelman, C.B. Williams, R.K. Phillips, Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. Br. J. Surg. 80 (12) (1993) 1618–1619.
[168] J. Burn, A.M. Gerdes, F. Macrae, J.P. Mecklin, G. Moeslein, S. Olschwang, et al., Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 4 (5) (2011) 655–665.
[169] P. Yang, Y. Zhou, B. Chen, H.W. Wan, G.Q. Jia, H.L. Bai, X.T. Wu, Aspirin use and the risk of gastric cancer: a meta-analysis. Dig. Dis. Sci. 55 (6) (2010) 1533–1539.
[170] L. Sun, S. Yu, Meta-analysis non-steroidal anti-inflammatory drug use and the risk of esophageal squamous cell carcinoma. Dis. Esophagus 24 (8) (2011) 544–549.
[171] X. Ye, J. Fu, Y. Yang, Y. Gao, L. Liu, S. Chen, Frequency-risk and duration-risk relationships between aspirin use and gastric cancer: a systematic review and meta-analysis. PLoS One 8 (7) (2013) e71522.
[172] N. Sivarasan, G. Smith, Role of aspirin in chemoprevention of esophageal adenocarcinoma: a meta-analysis. J. Dig. Dis. 14 (5) (2013) 222–230.
[173] B. Takkouche, C. Regueira-Mendez, M. Etminan, Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis. J. Natl. Cancer Inst. 100 (20) (2008) 1439–1447.
[174] Y.S. Zhao, S. Zhu, X.W. Li, F. Wang, F.L. Hu, D.D. Li, et al., Association between NSAIDs use and breast cancer risk: a systematic review and meta-analysis. Breast Cancer Res. Treat. 117 (1) (2009) 141–150.
[175] T. Luo, H.M. Yan, P. He, Y. Luo, Y.F. Yang, H. Zheng, Aspirin use and breast cancer risk: a meta-analysis. Breast Cancer Res. Treat. 131 (2) (2012) 581–587.
[176] S.W. Oh, S.K. Myung, J.Y. Park, C.M. Lee, H.T. Kwon, Aspirin use and risk for lung cancer: a meta-analysis. Ann. Oncol. 22 (11) (2011) 2456–2465.
[177] J. Xu, Z. Yin, W. Gao, L. Liu, R. Wang, P. Huang, et al., Meta-analysis on the association between nonsteroidal anti-inflammatory drug use and lung cancer risk. Clin. Lung Cancer 13 (1) (2012) 44–51.
[178] A.S. Neill, C.M. Nagle, M.M. Protani, A. Obermair, A.B. Spurdle, P.M. Webb, Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: a case-control study, systematic review and meta-analysis. Int. J. Cancer 132 (5) (2013) 1146–1155.
[179] W.H. Lo-Ciganic, J.C. Zgibor, C.H. Bunker, K.B. Moysich, R.P. Edwards, R.B. Ness, Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer. Epidemiology 23 (2) (2012) 311–319.
[180] L. Baandrup, M.T. Faber, J. Christensen, A. Jensen, K.K. Andersen, S. Friis, S.K. Kjaer, Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. Acta Obstet. Gynecol. Scand. 92 (3) (2013) 245–255.
[181] T.B. Huang, Y. Yan, Z.F. Guo, X.L. Zhang, H. Liu, J. Geng, et al., Aspirin use and the risk of prostate cancer: a meta-analysis of 24 epidemiologic studies. Int. Urol. Nephrol. (2014) .
[182] Y. Liu, J.Q. Chen, L. Xie, J. Wang, T. Li, Y. He, et al., Effect of aspirin and other non-steroidal anti-inflammatory drugs on prostate cancer incidence and mortality: a systematic review and meta-analysis. BMC Med. 12 (2014) 55.
[183] S.M. Fischer, E.T. Hawk, R.A. Lubet, Coxibs and other nonsteroidal anti-inflammatory drugs in animal models of cancer chemoprevention. Cancer Prev. Res. (Phila) 4 (11) (2011) 1728–1735.
[184] M.J. Thun, E.J. Jacobs, C. Patrono, The role of aspirin in cancer prevention. Nat. Rev. Clin. Oncol. 9 (5) (2012) 259–267.
[185] C. Stolfi, V. De Simone, V.F. Pallone, F.G. Monteleone, Mechanisms of action of non-steroidal anti-inflammatory drugs (NSAIDs) and mesalazine in the chemoprevention of colorectal cancer. Int. J. Mol. Sci. 14 (9) (2013) 17972–17985.
[186] N. Bhala, J. Emberson, A. Merhi, S. Abramson, N. Arber, J.A. Baron, et al., Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 382 (9894) (2013) 769–779.
[187] C. Varas-Lorenzo, N. Riera-Guardia, B. Calingaert, J. Castellsague, F. Salvo, F. Nicotra, et al., Myocardial infarction and individual nonsteroidal anti-inflammatory drugs meta-analysis of observational studies. Pharmacoepidemiol. Drug Saf. 22 (6) (2013) 559–570.
[188] M.A. Thorat, J. Cuzick, Role of aspirin in cancer prevention. Curr. Oncol. Rep. 15 (6) (2013) 533–540.
[189] S.R. Steinhubl, D.L. Bhatt, D.M. Brennan, G. Montalescot, G.J. Hankey, J.W. Eikelboom, et al., Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann. Intern. Med. 150 (6) (2009) 379–386.
[190] P. Gazzerro, M.C. Proto, G. Gangemi, A.M. Malfitano, E. Ciaglia, S. Pisanti, et al., Pharmacological actions of statins: a critical appraisal in the management of cancer. Pharmacol. Rev. 64 (1) (2012) 102–146.
[191] M. Osmak, Statins and cancer: current and future prospects. Cancer Lett. 324 (1) (2012) 1–12.
[192] P. Lochhead, A.T. Chan, Statins and colorectal cancer. Clin. Gastroenterol. Hepatol. 11 (2) (2013) 109–118.
[193] L. Corcos, C. Le Jossic-Corcos, Statins perspectives in cancer therapeutics. Dig. Liver Dis. 45 (10) (2013) 795–802.
[194] D.M. Boudreau, O. Yu, J. Johnson, Statin use and cancer risk: a comprehensive review. Expert Opin. Drug Saf. 9 (4) (2010) 603–621.
[195] S. Bonovas, K. Filioussi, N.M. Sitaras, Statin use and the risk of prostate cancer: a metaanalysis of 6 randomized clinical trials and 13 observational studies. Int. J. Cancer 123 (4) (2008) 899–904.
[196] X.D. Wu, K. Zeng, F.Q. Xue, J.H. Chen, Y.Q. Chen, Statins are associated with reduced risk of gastric cancer: a meta-analysis. Eur. J. Clin. Pharmacol. 69 (10) (2013) 1855–1860.
[197] P.P. Singh, S. Singh, Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. Ann. Oncol. 24 (7) (2013) 1721–1730.
[198] S. Singh, P.P. Singh, A.G. Singh, M.H. Murad, W. Sanchez, Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. Gastroenterology 144 (2) (2013) 323–332.
[199] S. Singh, A.G. Singh, P.P. Singh, M.H. Murad, P.G. Iyer, Statins are associated with reduced risk of esophageal cancer, particularly in patients with Barrett's esophagus: a systematic review and meta-analysis. Clin. Gastroenterol. Hepatol. 11 (6) (2013) 620–629.
[200] S. Bonovas, G. Nikolopoulos, N.M. Sitaras, Statins and reduced risk of hepatocellular carcinoma in patients with hepatitis C virus infection: further evidence is warranted. J. Clin. Oncol. 31 (32) (2013) 4160.
[201] D. Pradelli, D. Soranna, L. Scotti, A. Zambon, A. Catapano, G. Mancia, et al., Statins and primary liver cancer: a meta-analysis of observational studies. Eur. J. Cancer Prev. 22 (3) (2013) 229–234.
[202] T. Lytras, G. Nikolopoulos, S. Bonovas, Statins and the risk of colorectal cancer: an updated systematic review and meta-analysis of 40 studies. World J. Gastroenterol. 20 (7) (2014) 1858–1870.

[203] Y. Liu, W. Tang, J. Wang, L. Xie, T. Li, Y. He, et al., Association between statin use and colorectal cancer risk: a meta-analysis of 42 studies. Cancer Causes Control 25 (2) (2014) 237–249.
[204] Y. Liu, A. Qin, T. Li, X. Qin, S. Li, Effect of statin on risk of gynecologic cancers: a meta-analysis of observational studies and randomized controlled trials. Gynecol. Oncol. 133 (3) (2014) 647–655.
[205] F. Carrat, Statin and aspirin for prevention of hepatocellular carcinoma: what are the levels of evidence? Clin. Res. Hepatol. Gastroenterol. 38 (1) (2014) 9–11.
[206] Z.J. Zhang, Z.J. Zheng, H. Kan, Y. Song, W. Cui, G. Zhao, K.E. Kip, Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: a meta-analysis. Diabetes Care 34 (10) (2011) 2323–2328.
[207] R.J. Stevens, R. Ali, C.R. Bankhead, M.A. Bethel, B.J. Cairns, R.P. Camisasca, et al., Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials. Diabetologia 55 (10) (2012) 2593–2603.
[208] T.V. Kourelis, R.D. Siegel, Metformin and cancer: new applications for an old drug. Med. Oncol. 29 (2) (2012) 1314–1327.
[209] N.F. Col, L. Ochs, V. Springmann, A.K. Aragaki, R.T. Chlebowski, Metformin and breast cancer risk: a meta-analysis and critical literature review. Breast Cancer Res. Treat. 135 (3) (2012) 639–646.
[210] Z.J. Zhang, Z.J. Zheng, R. Shi, Q. Su, Q. Jiang, K.E. Kip, Metformin for liver cancer prevention in patients with type 2 diabetes: a systematic review and meta-analysis. J. Clin. Endocrinol. Metab. 97 (7) (2012) 2347–2353.
[211] B. Thakkar, K.N. Aronis, M.T. Vamvini, K. Shields, C.S. Mantzoros, Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: a meta-analysis using primary data of published studies. Metabolism 62 (7) (2013) 922–934.
[212] C.V. Rizos, M.S. Elisaf, Metformin and cancer. Eur. J. Pharmacol. 705 (1–3) (2013) 96–108.
[213] P. Zhang, H. Li, X. Tan, L. Chen, S. Wang, Association of metformin use with cancer incidence and mortality: a meta-analysis. Cancer Epidemiol. 37 (3) (2013) 207–218.
[214] Z.J. Zhang, Y. Bi, S. Li, Q. Zhang, G. Zhao, Y. Guo, Q. Song, Reduced risk of lung cancer with metformin therapy in diabetic patients: a systematic review and meta-analysis. Am. J. Epidemiol. 180 (1) (2014) 11–14.
[215] J. Kasznicki, A. Sliwinska, J. Drzewoski, Metformin in cancer prevention and therapy. Ann. Transl. Med. 2 (6) (2014) 57.
[216] S. Gandini, M. Puntoni, B.M. Heckman-Stoddard, B.K. Dunn, L. Ford, A. DeCensi, E. Szabo, Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer Prev. Res. (Phila) 7 (9) (2014) 867–885.
[217] A.A. Onitilo, J.M. Engel, I. Glurich, R.V. Stankowski, G.M. Williams, S.A. Doi, Diabetes and cancer II: role of diabetes medications and influence of shared risk factors. Cancer Causes Control 23 (7) (2012) 991–1008.
[218] M.S. McFarland, R. Cripps, Diabetes mellitus and increased risk of cancer: focus on metformin and the insulin analogs. Pharmacotherapy 30 (11) (2010) 1159–1178.
[219] I.M. Thompson, P.J. Goodman, C.M. Tangen, M.S. Lucia, G.J. Miller, L.G. Ford, et al., The influence of finasteride on the development of prostate cancer. N. Engl. J. Med. 349 (3) (2003) 215–224.
[220] G.L. Andriole, D.G. Bostwick, O.W. Brawley, L.G. Gomella, M. Marberger, F. Montorsi, et al., Effect of dutasteride on the risk of prostate cancer. N. Engl. J. Med. 362 (13) (2010) 1192–1202.
[221] F. Azzouni, J. Mohler, Role of 5alpha-reductase inhibitors in prostate cancer prevention and treatment. Urology 79 (6) (2012) 1197–1205.
[222] I.M. Thompson Jr., P.J. Goodman, C.M. Tangen, H.L. Parnes, L.M. Minasian, P.A. Godley, et al., Long-term survival of participants in the prostate cancer prevention trial. N. Engl. J. Med. 369 (7) (2013) 603–610.
[223] E.A. Klein, I.M. Thompson, Chemoprevention of prostate cancer: an updated view. World J. Urol. 30 (2) (2012) 189–194.
[224] G.S. Sandhu, K.G. Nepple, Y.S. Tanagho, G.L. Andriole, Prostate cancer chemoprevention. Semin. Oncol. 40 (3) (2013) 276–285.
[225] International Agency for Research on Cancer, IARC monographs on the evaluation of carcinogenic risks to humans. A Review of Human Carcinogens, Part D: Radiation, vol. 100D, WHO, Lyon, France, 2012.
[226] United Nations Scientific Committee on the Effects of Atomic Radiation, UNSCEAR 2006 Report: Sources and Effects of Ionizing Radiation. Report to the General Assembly, vol. 1, with Scientific Annexes A and B, United Nations, New York, 2008.
[227] International Commission on Radiological Protection (ICRP), ICRP Publication 103: Recommendations of the International Commission for Radiation Protection. International Commission on Radiological Protection, 2012.
[228] United Nations Scientific Committee on the Effects of Atomic Radiation, UNSCEAR 2000 Report: Sources and Effects of Ionizing Radiation. Report to the General Assembly, vol. 1: Effects, United Nations, New York, 2000.
[229] United Nations Scientific Committee on the Effects of Atomic Radiation, UNSCEAR 2008 Report: Sources and Effects of Ionizing Radiation. Report to the General Assembly with scientific annexes A and B, United Nations, New York, 2010.
[230] D.J. Brenner, R.E. Curtis, E.J. Hall, E. Ron, Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. Cancer 88 (2) (2000) 398–406.
[231] E. Ron, Cancer risks from medical radiation. Health Phys. 85 (1) (2003) 47–59.
[232] A. Stewart, J. Webb, D. Hewitt, A survey of childhood malignancies. Br. Med. J. 1 (5086) (1958) 1495–1508.
[233] R. Wakeford, Childhood leukaemia following medical diagnostic exposure to ionizing radiation in utero or after birth. Radiat. Prot. Dosim. 132 (2) (2008) 166–174.
[234] J.D. Boice Jr., D. Preston, F.G. Davis, R.R. Monson, Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Radiat. Res. 125 (2) (1991) 214–222.
[235] G.R. Howe, J. McLaughlin, Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. Radiat. Res. 145 (6) (1996) 694–707.
[236] M.M. Doody, J.E. Lonstein, M. Stovall, D.G. Hacker, N. Luckyanov, C.E. Land, Breast cancer mortality after diagnostic radiography: findings from the U.S. Scoliosis Cohort Study. Spine (Phila Pa 1976) 25 (16) (2000) 2052–2063.
[237] A. Berrington de González, S. Darby, Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. Lancet 363 (9406) (2004) 345–351.
[238] M.S. Pearce, J.A. Salotti, M.P. Little, K. McHugh, C. Lee, K.P. Kim, et al., Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 380 (9840) (2012) 499–505.
[239] J.D. Mathews, A.V. Forsythe, Z. Brady, M.W. Butler, S.K. Goergen, G.B. Byrnes, et al., Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 346 (2013) f2360.